

WHO clinical staging of HIV infection and disease, tuberculosis and eligibility for antiretroviral treatment: relationship to CD4 lymphocyte counts*

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SUMMARY

SETTING: Thyolo district, Malawi.

OBJECTIVES: To determine in HIV-positive individuals aged over 13 years CD4 lymphocyte counts in patients classified as WHO Clinical Stage III and IV and patients with active and previous tuberculosis (TB).

DESIGN: Cross-sectional study.

METHODS: CD4 lymphocyte counts were determined in all consecutive HIV-positive individuals presenting to the antiretroviral clinic in WHO Stage III and IV.

RESULTS: A CD4 lymphocyte count of ≤ 350 cells/ μ l was found in 413 (90%) of 457 individuals in WHO Stage III and IV, 96% of 77 individuals with active TB, 92% of 65 individuals with a history of pulmonary TB (PTB) in the last year, 91% of 89 individuals with a pre-

vious history of PTB beyond 1 year, 81% of 32 individuals with a previous history of extra-pulmonary TB, 93% of 107 individuals with active or past TB with another HIV-related disease and 89% of 158 individuals with active or past TB without another HIV-related disease. **CONCLUSIONS:** In our setting, nine of 10 HIV-positive individuals presenting in WHO Stage III and IV and with active or previous TB have CD4 counts of ≤ 350 cells/ μ l. It would thus be reasonable, in this or similar settings where CD4 counts are unavailable for clinical management, for all such patients to be considered eligible for antiretroviral therapy.

KEY WORDS: TB; HIV; CD4; ART; Malawi

THE ACQUIRED immune-deficiency syndrome (AIDS) is taking an appalling toll in Malawi, a small, impoverished country in Southern Africa. In 2003, it was estimated that there were 900 000 people living with human immunodeficiency virus (HIV) and AIDS, 87 000 AIDS-related deaths and 170 000 people in immediate need of antiretroviral therapy (ART).¹ However, in March 2004, only about 5000 people were currently accessing ART.² There is thus a desperate need to rapidly scale up treatment.

Initiation of ART is usually based on a measurement of the CD4 T-cell lymphocyte count, a laboratory test that acts as a 'proxy' for the immune status. The World Health Organization (WHO) recommends that ill HIV-positive persons who have a CD4 count < 350 cells/ mm^3 can be considered eligible for ART.³ However, this test is still expensive, the technology is sophisticated, and in resource-limited settings, tying the start of ART to a CD4 count measurement will act as a constraint to scaling up treatment. Recognising

these difficulties, the WHO has recommended that ART be given to all HIV-positive adults who are assessed clinically as being in WHO Clinical Stage III and IV, without the absolute requirement of a CD4 count.³

In this regard, tuberculosis (TB) poses a problem. HIV-positive patients with active pulmonary tuberculosis (PTB) or a history of PTB in the previous year are defined as WHO Stage III, and those with extra-pulmonary tuberculosis (EPTB) are defined as Stage IV.³ TB is a common HIV opportunistic infection in sub-Saharan Africa, and it is likely that many HIV-positive patients eligible for ART will have TB. However, HIV-positive patients in sub-Saharan Africa can present with smear-positive PTB across a wide spectrum of CD4 counts.^{4,5} We were concerned that many HIV-positive patients with TB might be started on ART with CD4 counts > 350 cells/ mm^3 , and thus be given treatment too early in the course of their HIV-related illness.

Thyolo district in southern Malawi is one of the

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pioneer districts in Malawi where the feasibility of offering ART in a routine programme setting is being assessed. CD4 lymphocytes were systematically counted in HIV-positive adults classified in WHO Stages III and IV, including patients with active and previous TB, to determine what proportion had CD4 counts $>$ or $<$ 350 cells/mm³, and we now report on this audit.

METHODS

Study setting and patient assessments

The study was carried out between April 2003 and January 2004 in Thyolo district, a rural region in southern Malawi with a population of 450 000. The main district hospital was the site of the study; this hospital has integrated voluntary counselling and HIV testing (VCT) units that have since 1999 offered services to patients, mothers attending antenatal care services and those who wish to know their HIV status. HIV testing is conducted using rapid whole blood test kits: Determine HIV-1/HIV-2 (Abbott Laboratories, Tokyo, Japan) and Uni-Gold™ HIV-1/HIV-2 (Trinity Biotech, Bray, Ireland), according to the WHO's strategy II for HIV antibody testing.⁶ Symptomatic HIV-positive individuals undergo a complete medical assessment for HIV-related diseases in the HIV clinic and are categorised into different WHO stages according to clinical findings.

ART and CD4 lymphocyte counts

ART, a fixed-dose combination of stavudine, lamivudine and nevirapine, is offered to patients in WHO Stage III and IV once their HIV-related disease has stabilised.⁷ CD4 lymphocyte counts are performed in all these patients, usually a week before the planned initiation of ART. CD4 lymphocyte counts were initially measured using a Coulter Cyto-Sphere CD4 Kit (Coulter Corporation, Hialeah, FL, USA) at the Blantyre Diagnostic Laboratories; since August 2003, CD4 lymphocytes have been counted using FacsCount® (Beckton Dickinson, Immunocytometry Systems, San Jose, CA, USA) at the John Hopkins Research Laboratory, Blantyre. Both laboratories are reference laboratories for the country, and they have strict quality control standards. The two techniques used for CD4 estimation are internationally acceptable, robust and are known to have a low average coefficient of variation (4–6%).^{8,9}

Study population and data collection

All HIV-positive individuals registered at the HIV/ART clinic between April 2003 and January 2004 and in WHO Stage III or IV were included in the study. Information on patients' demographic characteristics, WHO stage, CD4 count results and type of HIV-related disease was entered into a specific data collection sheet.

If a patient had active TB, the type of TB was

noted. If there was a past history of TB, specific inquiry was made about the type of TB, date of registration and initiation of anti-tuberculosis treatment and the HIV status at the time of last TB diagnosis. These data were verified through patient TB identity cards and TB registers. Since mid-1999, all newly registered TB patients in Thyolo have been offered VCT,¹⁰ and from that period on HIV status could be verified from the counselling registers. The current WHO staging system does not include individuals with a history of PTB beyond the past year or individuals with EPTB at any time in the past. In this study, HIV-positive individuals with a past history of PTB beyond 1 year were classified into WHO Stage III or IV according to the main HIV-related disease detected on initial clinical examination. Individuals with no other HIV-related disease except a past history of PTB beyond 1 year were classified as WHO Stage III, and those with a past history of EPTB were classified as Stage IV, irrespective of whether or not they had any other HIV-related disease.

Statistical analysis

Data were entered and analysed using Epi-Info software (Centers for Disease Control and Prevention, Atlanta, GA, USA). The level of confidence was set at 95%, and 5% error was used throughout.

RESULTS

Characteristics of the study population

Of 506 HIV-positive individuals, 457 were aged $>$ 13 years and were involved in the study. They included 127 (28%) men and 330 (72%) women, with a median age of respectively 34 (range 14–64) and 33 years (range 15–64); 338 (74%) were classified in WHO Stage III and 119 (26%) in Stage IV. Of these patients, 265 (58%) had active or past TB: 77 (17%) had active TB, 67 (15%) had a history of PTB in the past year, 89 (19%) had a history of PTB that dated beyond 1 year and 32 (7%) had a history of EPTB at some time in the past; 192 (42%) individuals had neither active TB nor a past history of TB.

CD4 profile in relation to WHO staging

Table 1 shows the CD4 profile in WHO Stage III or IV individuals. Of these, 413 (90%) had a CD4 count

Table 1 CD4 lymphocyte counts in relation to WHO clinical staging of HIV infection and disease

	CD4 $<$ 200 cells/ μ l n (%)	200–350 cells/ μ l n (%)	$>$ 350 cells/ μ l n (%)
WHO Stage III (n = 338)	232 (69)	77 (23)	29 (8)
WHO Stage IV (n = 119)	84 (71)	20 (17)	15 (12)
Total	316 (69)	97 (21)	44 (10)

WHO = World Health Organization; HIV = human immunodeficiency virus.

Table 2 CD4 lymphocyte counts in HIV-positive individuals with a history of active tuberculosis ($n = 77$)

	CD4 <200 cells/ μ l n (%)	200–350 cells/ μ l n (%)	>350 cells/ μ l n (%)
TB type			
Smear-positive PTB ($n = 31$)	25 (81)	5 (16)	1 (3)
Smear-negative PTB ($n = 30$)	24 (80)	5 (17)	1 (3)
Extra-pulmonary TB ($n = 16$)	11 (69)	4 (25)	1 (6)
Total	60 (78)	14 (18)	3 (4)

HIV = human immunodeficiency virus; TB = tuberculosis; PTB = pulmonary tuberculosis.

≤ 350 cells/ μ l, and 44 (10%) had >350 cells/ μ l. The median count for all individuals was 140 cells/ μ l (range 1–1314). In the 192 individuals with neither active TB nor a past history of TB, 173 (90%) had a CD4 count ≤ 350 cells/ μ l.

CD4 profile in individuals with active TB

Individuals with active TB had a median CD4 count of 133 cells/ μ l (range 1–715). The CD4 profile in relation to type of TB is shown in Table 2. Ninety-six per cent of HIV-positive individuals with active TB had a CD4 count ≤ 350 cells/ μ l.

CD4 profile in individuals with a history of PTB during the past year

Table 3 shows the CD4 profile in individuals with PTB during the past year. The median count in this group was 161 cells/ μ l (range 7–677), and 92% of all individuals had a CD4 count ≤ 350 cells/ μ l. There was no statistically significant difference in the proportion of individuals who had a CD4 count ≤ 350 cells/ μ l with regard to HIV status at the time of previous diagnosis of TB.

CD4 profile in individuals with a history of PTB over 1 year

Eighty-nine individuals had a history of PTB over 1 year previously (median 3.2, range 1.3–6.6 years).

Table 3 CD4 lymphocyte counts in individuals with a history of PTB in the previous 1 year and in relation to HIV status at the time of last TB diagnosis

	CD4 <200 cells/ μ l n (%)	200–350 cells/ μ l n (%)	>350 cells/ μ l n (%)
HIV-positive at last TB diagnosis			
Smear-positive PTB	23 (70)	9 (27)	1 (3)
Smear-negative PTB	15	4	1
HIV status unknown at last TB diagnosis			
Smear-positive PTB	8	5	0
Smear-negative PTB	24 (75)	3 (9)	5 (16)
Smear-positive PTB	11	2	1
Smear-negative PTB	13	1	4
Total	47 (73)	12 (19)	6 (8)

PTB = pulmonary tuberculosis; HIV = human immunodeficiency virus; TB = tuberculosis.

Table 4 CD4 lymphocyte counts in individuals with a history of PTB more than 1 year ago and in relation to HIV status at the time of last TB diagnosis

	CD4 <200 cells/ μ l n (%)	200–350 cells/ μ l n (%)	>350 cells/ μ l n (%)
HIV-positive at last TB diagnosis			
Smear-positive PTB	28 (70)	9 (23)	3 (7)
Smear-negative PTB	17	7	2
HIV status unknown at last TB diagnosis			
Smear-positive PTB	11	2	1
Smear-negative PTB	32 (65)	12 (24)	5 (10)
Smear-positive PTB	16	5	4
Smear-negative PTB	16	7	1
Total	60 (67)	21 (24)	8 (9)

PTB = pulmonary tuberculosis; HIV = human immunodeficiency virus; TB = tuberculosis.

The median CD4 count in these patients was 153 cells/ μ l (range 5–1126). In 81 (91%), CD4 counts were ≤ 350 cells/ μ l. HIV status was known at the time of TB diagnosis in 40 (45%). Table 4 shows the CD4 counts in relation to whether or not the HIV status was known at the time of last TB diagnosis. The difference between these two groups was not significant.

Of the 89 individuals, 75 (84%) had another HIV-related disease and 14 had no other HIV-related disease except previous PTB. Of those with another HIV-related disease, 60 were classified as WHO Stage III and 15 as Stage IV on the basis of the type of disease.

CD4 profile and WHO staging in individuals with a history of EPTB at any time in the past

The median CD4 count in this group was 113 cells/ μ l (range 19–1314); 81% of the 32 had a CD4 count ≤ 350 cells/ μ l (Table 5). The median time between the diagnosis of EPTB in the past and the present assessment was 2.6 years (range 1.2–14).

CD4 profile in relation to other HIV-related diseases in individuals with active TB and a past history of PTB or EPTB

The prevalence of HIV-related disease was significantly higher in individuals with a past history of PTB

Table 5 CD4 lymphocyte counts in individuals with a history of EPTB at any time in the past and in relation to HIV status at the time of last TB diagnosis

	CD4 <200 cells/ μ l n (%)	200–350 cells/ μ l n (%)	>350 cells/ μ l n (%)
HIV status			
Positive at last EPTB diagnosis ($n = 13$)	7 (54)	3 (23)	3 (23)
Unknown at last EPTB diagnosis ($n = 19$)	12 (63)	4 (21)	3 (16)
Total	19 (59)	7 (22)	6 (19)

EPTB = extra-pulmonary tuberculosis; HIV = human immunodeficiency virus; TB = tuberculosis.

Table 6 CD4 lymphocyte counts in relation to the presence or absence of an opportunistic infection in patients with active TB or a past history of TB

	CD4 <200 cells/ μ l n (%)	200–350 cells/ μ l n (%)	>350 cells/ μ l n (%)	Total n (%)
Active TB (n = 77)				
Opportunistic infection present	5 (83)	1 (17)	0	6 (8)
Opportunistic infection absent	55 (78)	13 (18)	3 (4)	71 (92)
PTB <1 year (n = 67)				
Opportunistic infection present	6 (75)	2 (25)	0	8 (12)
Opportunistic infection absent	41 (70)	10 (17)	8 (13)	59 (88)
PTB >1 year (n = 89)				
Opportunistic infection present	56 (75)	15 (20)	4 (5)	75 (84)
Opportunistic infection absent	4 (29)	6 (43)	4 (29)	14 (16)
EPTB at any time in the past (n = 32)				
Opportunistic infection present	10 (56)	4 (22)	4 (22)	18 (56)
Opportunistic infection absent	9 (64)	3 (21)	2 (14)	14 (44)

TB = tuberculosis; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis.

over 1 year (87%) and with EPTB (56%) than in those with active TB (8%) or a history of PTB during the past year (12%). The CD4 profiles in relation to these different groups are shown in Table 6. The majority of individuals with active TB or a past history of PTB (during or beyond the past year) as well as those with a history of EPTB at any time in the past had CD4 counts ≤ 350 cells/ μ l, irrespective of whether or not they had an HIV-related disease.

DISCUSSION

This study shows that if ART was initiated only on clinical grounds, at least nine of 10 HIV-positive individuals in WHO Stage III and IV would have CD4 counts ≤ 350 cells/ μ l and would thus be eligible for ART. The great majority of individuals with active TB as well as a past history of PTB and EPTB would also have CD4 counts ≤ 350 cells/ μ l, and would similarly be eligible for ART. About 10% of those in our setting had a CD4 count > 350 cells/ μ l. In the absence of routine CD4 counting, these cases would have started ART at an earlier time than is usually recommended.

There were 188 individuals, 42% of those in WHO Stage III and IV, who presented to the ART clinic with a past history of TB; such patients appear to be a privileged group in terms of an entry-door to ART. Since early 1999, all HIV-positive individuals, including TB patients, have been integrated into a community network of home-based care (HBC) volunteers and nurses.¹⁰ This network ensures that individuals are made aware of the link between TB and HIV and

are informed about ART eligibility. Individuals with active and past TB are also encouraged to present to the ART clinic. It is likely that our network of HBC volunteers and nurses facilitated the selection and referral of individuals with a past history of TB to the ART clinic, and the fact that 87 (46%) patients with a past history of TB had no other HIV-related disease on presentation supports the hypothesis that it is TB that brought them to the clinic.

Individuals with a past history of PTB dating from beyond 1 year and a history of EPTB at any time in the past are not currently included in the WHO classification, and by strict definition they are not eligible for ART.³ We think this should be re-examined. First, we had documented evidence (through TB cards and counselling registers) that nearly half (47%) of all individuals in these two groups were HIV-positive at the time of their last TB diagnosis. If ART had been available at the time, they would in theory have been eligible for ART and would have been started on treatment. These individuals are also likely to have had a downhill progression in immune status since their last episode of TB, and the significantly higher prevalence of other HIV-related diseases in these two groups of HIV-positive individuals is thus unsurprising. The majority of individuals with a past history of PTB beyond 1 year and with EPTB at any time in the past had a CD4 count ≤ 350 cells/ μ l. Second, HIV prevalence in TB patients in Thyolo is 77%,⁵ and close to 60% of all HIV individuals presenting in WHO Stage III or IV had active TB or a past history of TB. It is thus likely that TB is often what brings HIV-positive individuals to medical attention. In such settings, it would seem reasonable to think that a considerable proportion of HIV-positive individuals with a past history of TB are likely to have been HIV-positive at the time of their last TB diagnosis. Third, a past diagnosis of TB is in practice a clear WHO defining event that can be verified through patient TB identity cards and TB registers. In resource-poor settings such as ours, this is often not the case with many other WHO Stage III and IV clinical conditions.

This study supports WHO clinical staging as an appropriate method for deciding whom to start on ART. Reassuringly, the majority of HIV-positive patients with active or previous TB had low CD4 counts, ≤ 350 cells/ μ l, and were thus eligible for ART based on international criteria. This is useful for scaling up ART in resource-limited settings such as Malawi, where services will inevitably have to be provided at lower levels of the health infrastructure to ensure equitable access for the poor.

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RÉSUMÉ

CONTEXTE : District de Thyolo au Malawi.

OBJECTIFS : Déterminer les décomptes de lymphocytes CD4 chez les patients séropositifs pour le VIH, âgés de plus de 13 ans et classifiés comme stades III et IV de la classification clinique de l'OMS et chez les patients atteints de tuberculose (TB) active ou antérieure.

SCHEMA : Etude transversale.

MÉTHODES : Les décomptes de lymphocytes CD4 ont été faits chez tous les individus consécutifs séropositifs pour le VIH aux stades III et IV de l'OMS, se présentant dans une polyclinique antirétrovirale

RÉSULTATS : On a trouvé un décompte de lymphocytes CD4 de ≤ 350 cellules/ μL chez 413 (90%) des 457 individus aux stades III et IV de l'OMS, chez 96% de 77 individus atteints de TB active, chez 92% des 65 individus avec des antécédents de tuberculose pulmonaire (TBP)

au cours de la dernière année, chez 91% des 89 individus ayant des antécédents de TBP remontant à plus d'un an, chez 81% des 32 individus avec une anamnèse de TB extrapulmonaire, chez 93% de 107 individus atteints d'une TB active ou stabilisée et qui étaient atteints d'une autre maladie en relation avec le VIH et chez 89% de 158 individus atteints d'une TB active ou stabilisée mais sans autre maladie en relation avec le VIH.

CONCLUSIONS : Dans notre contexte, neuf sur 10 individus séropositifs pour le VIH se présentant aux stades III et IV de l'OMS ou avec une TB active ou antérieure ont des décomptes de lymphocytes CD4 ≤ 350 cellules/ μL . Il serait dès lors raisonnable dans des contextes similaires où les décomptes de CD4 ne sont pas disponibles de considérer dans la prise en charge clinique l'ensemble de ces patients comme éligibles pour le traitement antirétroviral.

RESUMEN

MARCO DE REFERENCIA : El distrito de Thyolo, Malawi.
OBJETIVOS : Determinar el recuento de linfocitos CD4 en pacientes mayores de 13 años con serología positiva para el VIH que se encuentran en estadio clínico III o IV según la clasificación de la OMS, y en pacientes con tuberculosis (TB) activa o con antecedente de TB.

DISEÑO DEL ESTUDIO : Estudio transversal.

MÉTODOS : Se determinó el recuento de linfocitos CD4 en todos los individuos seropositivos que se presentaron en estadios III o IV de la OMS al consultorio de tratamiento antirretrovírico.

RESULTADOS : Se observó un recuento de linfocitos CD4 ≤ 350 células/ μL en 413 de los 457 pacientes (90%) en estadios III o IV de la OMS, en el 96% de los 77 individuos con TB activa, en el 92% de los 65 individuos con antecedente de TB pulmonar en el último año, en el

91% de los 89 pacientes con antecedente de más de 1 año de TB pulmonar, en el 81 % de los 32 individuos con antecedente de TB extrapulmonar, en el 93 % de los 107 individuos con antecedente de TB o con TB activa con otra enfermedad relacionada con la infección por el VIH y en el 89 % de los 158 pacientes con antecedente de TB o con TB activa sin otra enfermedad relacionada con la infección por el VIH.

CONCLUSIONES : En nuestro medio, nueve de cada 10 individuos seropositivos que acuden en estadio clínico III o IV de la OMS con TB activa o antecedente de TB tienen recuentos de CD4 ≤ 350 células/ μL . En este contexto, o en ambientes similares donde no se dispone del recuento de CD4 para el manejo clínico, sería razonable considerar todos estos pacientes idóneos para tratamiento antirretrovírico.